A METHOD OF PRECISION CANCER THERAPY

FIELD OF THE INVENTION

[0001] The present invention relates to a method of treatment of cancer, said method comprising administering an effective dose of a protein kinase inhibitor to a patient in need thereof having said cancer. The present invention also relates to a method of post-transcriptional control of cancer-related genes comprising administering an effective amount of a protein kinase inhibitor to a subject in need thereof. The present invention further relates to a method of identifying a protein kinase inhibitor for normalizing post-transcriptional regulation as precision cancer therapy.

BACKGROUND OF THE INVENTION

[0002] Cancers are a diverse variety of pathological conditions. One example is breast cancer (BC) which is the most common form of female malignancies, representing a major cause of death from cancer among the women worldwide. Breast cancer is characterized by alteration in the expression of many genes involved in cell cycle, growth and differentiation, DNA repair, apoptosis, inflammation, angiogenesis, invasiveness, and metastasis.

[0003] Gene expression is regulated by different mechanisms, including transcriptional, post-transcriptional, and post-translational modification mechanisms. Post-transcriptional control represents an essential level of gene expression fine tuning and comprises processes such as mRNA decay, mRNA transport, and translation. mRNA decay affects the level of available mRNA for translation and it is a tightly regulated process that mainly relies on the presence of a cis-acting sequence in the primary transcript of the mRNA to which trans-acting proteins bind and confer stability or instability of the mRNA.

[0004] Among the well-known and extensively studied cis-acting mRNA instability determinants are adenylate-uridylate-rich elements (AU-rich elements, AREs). Several ARE binding proteins (ARE-BP) are involved in the pathogenesis of cancer. Specifically, many human tumors are found be associated with deficiency of tristetraprolin (TTP, ZFP36) and/or overexpression of human antigen R (HuR). The aberrant expression of these proteins can derive from misregulation on various regulational levels including transcriptional regulation, epigenetic regulation, post-transcriptional regulation, and post-translational regulation.

[0005] Phosphorylation of ARE-BPs by different protein kinases is a mechanism of post-translational modification that highly affects the cellular localization and activity of said ARE-BPs. Protein phosphorylation results in alteration of protein structure and conformation, and modifies its activity and function. The commonly phosphorylated amino acids in eukaryotes are serine, threonine, and tyrosine. The phosphorylation is mediated through the action of a protein kinase (PK), and can be reverse through the action of a phosphatase. Nearly 2% of the human genome encode for PKs, representing about 538 genes which are subdivided into typical, or conventional, and atypical protein kinases, according to the kinase database (http://kinase.com/kinbase/). The majority of typical PKs phosphorylates serine/threonine (STPKs) and only a minority of PKs phosphorylates tyrosine, and atypical PKs are mostly STPKs. To date, FDA has approved 37 small molecule kinase inhibitors and many others are in phase-2/3 clinical trials. Most of the approved kinase drugs are intended for treatment of cancers, and only few of them have been approved for treatment of non-cancerous conditions, such as sirolimus for organ rejection.

[0006] Polo-like kinases (PLKs) are a family of regulatory serine/threonine kinases comprising five members including polo-like kinase 1 (PLK-1), as well as PLK-2, PLK-3, PLK-4, and PLK-5. Polo-like kinases are involved in the cell cycle at various stages, including mitosis, spindle formation, cytokinesis, and meiosis. Beyond cell cycle regulation, there is evidence that PLKs play regulatory roles in different cellular pathways and an increasing amount of PLK substrates is revealed. For example, PLK-1 has been found to phosphorylate insulin receptor substrate (IRS), β-catenin, heat-shock protein 70, mTOR, vimentin, and the breast cancer susceptibility protein (BRCA2).

[0007] Regulating aberrant expression of cancer-related genes using ARE-BPs is a potential approach for a method of treatment of cancer.

[0008] US 2010/0055705 A1 discloses compositions and methods for diagnosing and treating cancer, including TTP as a biomarker and therapeutic option for the treatment of cancer.

[0009] EP 2 435 041 B1 relates to a therapeutic combination comprising a PLK-1 inhibitor and an antineoplastic agent.

[0010] Bhola et al. [1] disclose a kinome-wide functional screen identifying a role of PLK-1 in acquired hormone-independent growth of ER^+ human breast cancer.

[0011] Maire et al. [2] relates to a PLK-1 inhibitor as potential therapeutic option for the management of patients with triple-negative breast cancer.

[0012] However, a method of treatment of cancer involving post-transcriptional control of expression of cancer-related genes, comprising administering a protein kinase inhibitor for normalizing the levels of TTP and HuR, has not been described. Thus, the present invention aims at a method of treatment of cancer, wherein said cancer is characterized by aberrant expression of cancer-related genes and/or ARE-BPs.

[0013] The present inventors have used a commercially available kinase inhibitor library that comprises 378 drugs comprising FDA approved agents. High-throughput screening was performed using said library by conducting an optimized highly selective post-transcriptional reporter assay that was designed to identify hits affecting ARE-mediated post-transcriptional regulation. Compounds from the PK inhibitor library were scored as hits if they reduced the expression of ARE-containing reporter activity compared to control reporter activity. The present inventors disclose a method of treatment of cancer using ARE-mediated post-transcriptional regulation of gene expression involving administering a protein kinase inhibitor, namely a B-Raf kinase inhibitor, VEGFR2 inhibitor, or a polo-like kinase inhibitor, preferably a polo-like kinase 1 inhibitor, to a patient in need thereof.

SUMMARY OF THE INVENTION

[0014] In the following, the elements of the invention will be described. These elements are listed with specific embodiments, however, it should be understood that they may be combined in any manner and in any number to create additional embodiments. The variously described examples